The Impact of Pleural Lavage Cytology Before and After Resection on Prognosis

Rezeksiyon Öncesi ve Sonrasında İncelenen Plevral Lavaj Sitolojisinin Prognoza Etkisi

Lung Cancer and Pleural Lavage Cytology

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Özet

Amaç: Plevral sıvı sitolojisinde tümör hücresi saptanması malignite açısından ileri evre ve kötü prognoz göstergesidir. Çalışmamızda plevral sıvısı olmayan operabl malignite olgularında peroperatif plevral lavaj ile saptanabilecek tümör pozitifliğinin kitle ve mediastinal lenf nodu özelliklerine göre analizi amaçlanmıştır. Gereç ve Yöntem: Küçük hücrteli dışı akciğer kanseri nedeni ile opere edilen 199 olguda, diseksiyon öncesi ve rezeksiyon sonrası yapılan plevral lavajın sitolojik değerlendirme sonuçları cinsiyet, lezyon şekil ve boyutu, toraks bilgisayarlı tomografi ve Pozitron emisyon tomografisi (PET BT) lenf nodu tutulumu, lezyonun SUVmax değeri, lokalizasyonu, patolojik N1 ve N2 metastazı, lokal invazyon, tümörün histopatolojisi gibi değişkenler ile istatistiksel olarak karşılaştırıldı. Bulgular: Çalışmaya dahil edilen olgular 4 yıl takip edildi. On (%5) olguda tümör nüksü, 12 (%6) olguda uzak organ metastazı saptandı. Çok değişkenli analizde ilk lavaj sitolojisi ile uzak organ metastazı arasında ve son lavaj sitolojisi ile tümör nüksü arasında anlamlı ilişki saptanmıştır. Postoperatif uzak organ metastazının lenf nodu metastazı ve ilk lavaj sitoloji pozitifliği ile, tümör nüksünün PET BT lenf nodu tutulumu, lenf nodu metastazı ve son plevral lavaj sitoloji pozitifliği ile anlamlı düzeyde ilişkisi saptanmıştır. Tartışma: Günümüzde plevral lavaj analizi ile ilgili çalışmalarda artışlar söz konusu olup lavaj zamanlaması ve örnek alımı ile ilgili standardizasyona ihtiyaç mevcuttur. Daha geniş seriler içeren çok merkezli çalışmalar sonucunda pozitif lavaj sitolojisinin evrelendirmede tıpkı malign efüzyon gibi prognostik faktör olarak kabul edileceğini umuyoruz.

Anahtar Kelimeler

Akciğer Kanseri; Plevral Lavaj; Sitoloji; Prognoz

Abstract

Aim: Regardless of pleural effusion, presence of tumor in pleural cavity indicates presence of more aggressive tumor. In this study, we analysed positive tumor results in preoperative pleural lavage in operable malignant cases with no pleural fluid according to the mass and mediastinal lymph node characteristics. Material and Method: Pleural lavage before preoperative dissection and after resection was performed on 199 cases that underwent surgery for non small cell lung cancer (NSCLC). Findings of lavage were statistically evaluated based on gender, lesion shape and size, lymph node involvement in positron emission tomography- computed tomography (PET-CT), SUV-max value of lesion, localisation of the lesion, N1 and N2 metastases, local invasion findings, histopathological type of tumor and type of resection. Results: Cases included in this study were followed for four years. Ten of the cases (5%) had tumor recurrence and 12 of them (6%) had distant organ metastasis. In multivariable analysis, significant correlation was found between the first positive pleural lavage cytology and postoperative distant organ metastasis; the last pleural lavage cytology and tumor recurrence; postoperative distant organ metastasis and lymph node metastasis and the first positive lavage cytology; tumor recurrence and PET-CT lymph node uptake, lymph node metastasis and the last positive pleural lavage cytology. Discussion: Recently there has been an increase in studies on pleural lavage analysis and there is a need for standardization in lavage timing and sampling. We hope that positive lavage cytology, like malign effusion, will be accepted as a prognostic factor in staging as more studies based on wider series are conducted.

Keywords

Lung Cancer; Pleural Lavage; Cytology; Prognosis

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Introduction

Conducting tests for metastasis is a key aspect of lung cancer treatment before the surgery. Detection of malignant pleural effusion indicates poor prognosis. On the other hand, the first intraoperative pleural lavage study conducted in 1958 with 49 cases demonstrated for the first time that there could be tumor cells in pleural cavity in cases with no macroscopic pleural effusion or pleural invasion [1]. Many studies emphasized the significance of pleural lavage in planning lung cancer treatment [2-7]. In existing studies, positive pleural lavage cytology after thoracotomy have been calculated as 4-14% [2-4,6,8,9]. Regardless of pleural effusion, presence of tumor in pleural cavity indicates presence of more aggressive tumor. In this study, we analysed positive tumor results in preoperative pleural lavage in operable malignant cases with no pleural fluid according to the mass and mediastinal lymph node characteristics. Even if pleural lavage examination is not a routine part of lung cancer surgery, there is a need for further studies in this field.

Material and Method

Pleural lavage before preoperative dissection and after resection was performed on 199 cases that underwent surgery for non small cell lung cancer (NSCLC) in the thoracic surgery clinic of our hospital. Before the dissection stage after thoracotomy, the thoracic cavity was washed with 200 cc serum physiologic fluid touching all pleural and parenchymal surfaces and the fluid in the cavity was aspirated for cytopathological examination. Following the resection and dissection of mediastional lymph node, lavage was performed again with 200 cc serum physiologic fluid. Both of the fluids obtained have been cytopathologically examined. Cytopathological results were compared with features of lesions. All of the cases were examined with computed tomography (CT) in preopreative stage. The cases with suspected N2 lymph node and distant organ metastasis after the CT were examined with positron emission tomography (PET-CT). Carcinoembryonic antigen (CEA) levels in the blood were measured in preoperative stage in all cases. Lung resection and mediastinal lymph node dissection were performed in cases, which did not have N2 lymph node and distant organ metastasis in PET-CT, depending on the localisation of tumor. Pleural lavage was performed in all cases that underwent surgery. Findings of lavage were statistically evaluated based on gender, lesion shape and size, lymph node involvement in PET-CT, SUV-max value of lesion, localisation of the lesion, N1 and N2 metastases, local invasion findings, histopathological type of tumor and type of resection.

The relation between cytological examination results for the lavage fluid taken before dissection and after resection and other prognostic factors were analysed using SPSS, Mann Whitney U and Chi square and correlation test between different variables.

Results

Of the 199 cases, 176 (88,4%) are male, 23 are female with an average age of 59,69±9,558 (27-80). Ninety-six of the cases (%48,2) had squamous cell carcinoma, 60 cases (30,2%) had adenocarcinoma and 43 cases (21,6%) had other types of histological malignancies. Eighty nine of the detected malignancies (44,7%) were located within the right hemithorax, 110 of them (55,3%) were located on the left. Average Fludeoxyglucose (FDG) uptake of all cases was calculated as 12,02±5,718 in PET-CT. Hundred and forty-three of the lesions (71,9%) had irregular margins, 40 of them (20,1%) lobulated, 12 of them (6%) spiculated, 4 of them (2%) had smooth margins. In preoperative examination, FDG uptake was detected in N1 lymph nodes of 144 cases (%72,4). For these malignancies, 18 (9%) sublobar resection, 113 (56,8%) lobectomy, 20 (10%) bilobectomy, 45 (22,6%) pneumonectomy were performed. Following postoperative histopathological examination, N1 metastasis was identified in 45 cases (22,6%), N2 metastasis was identified in 10 cases (5%) and both N1 and N2 metastases were identified in 17 cases (8,5%). 115 cases (57,8%) had tumors due to local invasion. Average CEA values for the cases were calculated as 8,95±2,866 (0,59-332,91).

While many of the cases (38,7%) were in the 7th decade, one of the cases (0,5%) was in the 3rd decade. Based on the classification according to tumor diameter, T2a (35,2%) and T1b (24,6%) cases were identified as the ones that underwent surgery most often. According to TNM staging system, it was mostly Stage IIA (29,1%) and Stage IA (27,1%) cases. Based on the examination of FDG uptake in PET/CT, it was observed that cases with SUVmax values between 10-15 constituted 33,2% of the cases. Cases included in this study were followed for four years. Ten of the cases (5%) had tumor recurrence and 12 of them (6%) had distant organ metastasis.

In 38 cases (19,1%), tumor cells were detected in pleural lavage fluid taken before preoperative dissection and in 15 cases (7,5%) tumor cells were detected in pleural lavage fluid taken after resection. Positive results after the lavage cytology were examined according to age, gender, serum CEA level, SUVmax levels of the mass in PET-CT, positive PET-CT of the mediastinal lymph nodes, surgery type, pathological type of mass, metastasis of lymph nodes, findings of local invasion of tumor, pathological stage, margin of the mass, tumor recurrence after the surgery, distant organ metastasis, and recovery (Table 1).

It was statistically shown that there is a significant correlation between the first positive lavage fluid taken before dissection and postoperative distant organ metastasis, and between the last positive lavage fluid and tumor recurrence (Table 2).

Despite the initial positive results in lavage cytology in 30 cases with irregular margins, 30 cases with high uptake in PET-CT, 20 cases with squamous cell carcinoma, 14 cases with FDG SUVmax value between 10-15 in PET-CT, 17 cases with serum CEA value<2,5, 14 cases in stage IIA, 17 cases with visceral pleural invasion, and 14 cases and T2a cases, no statistical significance was found.

Likewise, despite the positive results in lavage cytology in 10 cases with irregular margins, 13 cases with high uptake in PET-CT, 9 cases with squamous cell carcinoma, no statistical significance was found.

Tumor recurrence occurred in 10 cases included in this study and malign tumors were detected in distant organs in 12 cases in later periods. According to the histopathological examination of these cases, these tumors were interpreted as lung cancer metastasis. In examination of the cases with tumor recurrence, significant correlation was found between PET-CT lymph node involvement, lymph node metastasis and last lavage cytology

fluid (Table 3). Significant correlation was found in the first positive cytology and distant organ metastasis.

Discussion

Lung cancer is the leading cause of cancer death. The best known treatment is complete removal of the tumor. Five year survival rate after the full resection in the early stages is above 80%. Following the diagnosis of lung cancer, correct staging of the cancer is crucial in order to identify patients who would benefit from a surgery, to avoid unnecessary surgeries and to decide the best treatment option [10].

In lung cancer staging, TNM staging system is used. TNM staging enables identification of prognosis, treatment planning, evaluation of treatment results and standard information exchange between different centres [11,12]. Imaging methods prove the most important non-invasive method in lung cancer staging. PET-CT is valued as better compared to CT and MR in N staging which one of the main parameters in staging [13,14]. PET/CT is used for initial staging of the tumor, to evaluate response to treatment, to detect residual and recurrent disease after the treatment in lung malignancies [15]. In many studies it is emphasized that there is a correlation between FGD uptake and tumor growth rate, aggressiveness and proliferation capacity. FDG uptake is considered as an independent prognostic factor, which correlates with survival rates in lung cancer cases, especially in earlier stages. It is also argued that higher SUVmax values meant higher tumor proliferation capacity and poorer prognosis [16]. Recent studies based on series show that there is a correlation between PET-CT and tumor diameter [17,18]. In this study, which is a similar one, significant correlation was found between tumor diameter and lymph node involvement in PET-CT. Besides, SUVmax value of mass had positive correla-

Table 1. Evaluation of first and last lavage cytology positivity and other prognostic factors

				First lavage			Last lavage		
		N	%	Positive cytology (N)	Group %	Categorical %	Positive cytology (N)	Group %	Categorical %
Gender	Male	176	88,4	33	86,8	18,7	14	93,3	7,9
	Female	23	11,6	5	13,1	21,7	1	6,6	4,3
Tumor edge	Irregular	143	71,9	30	78,9	20,9	10	66,6	6,9
	Lobulated	40	20,1	5	13,1	12,5	3	20	7,5
	Spiculated	12	6	2	5,2	16,6	1	6,6	8,3
	Smooth	4	2	1	2,6	25	1	6,6	25
PET/CT Lymph node	No uptake	55	27,6	8	21	14,5	2	13,3	3,6
	Uptake	144	72,4	30	78,9	20,8	13	86,6	9
Side	Right	89	44,7	19	50	21,3	8	53,3	8,9
	Left	110	55,3	19	50	17,2	7	46,6	6,3
Lymph node metastasis	No metastasis	127	63,8	19	50	14,9	9	60	7
	N1	45	22,6	12	31,5	26,6	4	26,6	8,8
	N2	10	5	4	10,5	40	0	0	0
	N1+N2	12	8,5	3	7,8	25	2	13,3	16,6
Local invasion	No invasion	84	42,2	15	39,4	17,8	7	46,6	8,3
	Visceral pleura	70	35,2	17	44,7	24,2	5	33,3	7,1
	Parietal pleura	26	13,1	3	7,8	11,5	2	13,3	7,6
	Perihilar adipose tissue	16	8	3	7,8	18,7	1	6,6	6,2
	Thoracic wall	3	1,5	0	0	0	0	0	0
Diagnosis	Adenocarcinoma	60	30,2	12	31,5	20	5	33,3	8,3
	SCC	96	48,2	20	52,6	20,8	9	60	9,3
	Other	43	21,6	6	15,7	13,9	1	6,6	2,3
Resection type	Sublobar	18	9	2	5,2	11,1	4	26,6	22,2
	Lobectomy	113	56,8	24	63,1	21,2	6	40	5,3
	Bilobectomy	20	10	3	7,8	15	1	6,6	5
	Pneumonectomy	45	22,6	9	23,6	20	4	26,6	8,8
	Ekstraparenchymal	3	1,5	0	0	0	0	0	0
Stage	IA	54	27,1	6	15,7	11,1	5	33,3	9,2
	IB	34	17,1	7	18,4	20,5	3	20	8,8
	IIA	58	29,1	14	36,8	24,1	3	20	5,1
	IIB	22	11,1	1	2,6	4,5	2	13,3	9
	IIIA	31	15,6	10	26,3	32,2	2	13,3	6,4
Tumor recurrence	Yes	10	5	4	10,5	40	3	20	30
	No	189	95	34	89,4	17,9	12	80	6,3
Distant metastasis	Yes	12	6	6	15,7	50	1	6,6	8,3
	No	187	94	32	84,2	17,1	14	93,3	7,4

tion with pathological stage, tumor diameter and gender.

TNM staging is one of the most important methods in identifying prognosis in lung cancer [12-19]. Certain clinical factors impact on prognosis regardless of the cancer stage. Studies in recent years show that intraoperative pleural lavage cytology is an effective prognostic factor in resectable lung cancers [6]. It is argued that exfoliation of tumor cells into pleural cavity through subpleural lymphatic and veins causes positive results in pleural lavage before resection. So, pleural lavage performed before lung resection can be used to identify whether tumor cells spread in pleural cavity. Buhr et al argued that significant correlation was found between positive pleural lavage cytology before resection and pleural invasion [20]. Nagawara et al also had similar findings and argued that in cases with positive cytology there is an increase of risk of pleural invasion and recurrence [21]. Our study showed that pleural and perhilar region invasion did not affect lavage cytology. However positive correlation was found between local invasion and tumor diameter. It is recommended that this situation must be evaluated during the pathological staging together with the findings obtained as a result of the studies analysing the impact of positive lavage cytology on prognosis. In a study published in 1999, Okada et al stated that 18 of the 482 cases with no pleural effusion had positive results in pleural lavage cytology performed after thoracotomy and that 5 year survival rate in patients with positive pleural lavage before resection was 14,6% and 52,9% in patients with negative pleural lavage [2]. In another study, Dresler et al argued that 14% of the patients who underwent pleural lavage before resection had malign cells in lavage cytology and that these patients had poor prognosis [7]. In a similar study conducted by Ichinose et al in 2001 based on 1890 patients, tumor cells were detected in 147 patients (7,8%) in pleural cytology and it was emphasized that prognosis was worse in Stage I and Stage II patients with positive pleural lavage compared to patients with negative lavage [6].

In our study, 43 cases had positive lavage cytology and tumor cells were detected in 38 cases (19,1%) in pleural lavage fluid taken before resection preoperatively and in 15 cases (7,5%) in lavage fluid taken after resection. 28 cases in which tumor cells were detected in the first lavage examination had negative cytology results, and 5 cases which had negative cytology in the first lavage had positive last lavage cytology. The analysis of first lavage fluid and other prognostic factors showed statistically significant correlation with distant organ metastasis and the analysis of the last lavage fluid showed statistically significant correlation with tumor recurrence. Another prognostic factor in lung cancer is the tumor margin or edges and studies show that there is a morphological feature which is directly related to prognosis. Meniga et al stated that patients with smooth tumor edges had higher survival rate compared to those with speculated tumor edge. They argue that relative risk of death is 4-11 times higher in patients whose tumors had spiculated edges compared to those whose tumors had smooth edges [22]. In our study, 7,9% of the patients had tumors with irregular edges, 20,1% lobulated edges and 6% spiculated edges. After a comparison with the lavage cytology, it was statistically found that tumor edge does not affect cytology results. However significant correlation was found between tumor edge and resection type. It was found that 90% of the cases that underwent bilobectomy had tumors with irregular edge.

Many scholars argue that exfoliation of tumor cells from metastatic lymph nodes into pleural cavity after surgical manipulations lead to positive cytology after lung resection [23,24]. Although the reason for positive cytology is not yet fully known, we do not think that this theory is completely valid. Because in our study we found no meaningful correlation between neither the first nor the last positive lavage fluid and metastatic lymph node, and positive local invasion does not affect lavage cytology.

Table 2. Statistical analyses of first and last lavage cytology positivity and other prognostic factors

	Mann-Whitney U	
	First lavage	Last lavage
PET/CT Lymph node uptake	0,31	0,19
Tumor diameter	0,82	0,43
Tumor edge	0,32	0,56
SUVmax value	0,3	0,58
Side	0,46	0,48
Resection type	0,09	0,49
Pathological diagnosis	0,5	0,32
Lymph node metastasis	0,06	0,75
Local invasion	0,57	0,64
CEA value	0,11	0,98
Pathological stage	0,1	0,59
Distant metastasis	0	0,91
Tumor recurrence	0,08	0
Tumor diameter stage	0,85	0,42

Table 3. Correlation analysis of prognostic factors associated with malignancy

SUVmax	,019	,000	,961										
Resection type	,451	,207	,011	,600	,404	,004							
LN metastasis	,005	,410	,212	,874	,302	,227	,512						
Local invasion	,860	,028	,759	,302	,434	,692	,613	,012					
T stage	,721	,000	,131	,000	,048	,660	,040	,095	,007	,989	,598		
SUV group	,092	,001	,922	,000	,750	,477	,591	,269	,066	,467	,695	,000	
CEA group	,017	,445	,622	,204	,166	,174	,320	,653	,252	,062	,922	,868	,567
P stage	,554	,000	,874	,020	,305	,301	,045	,000	,002	,088	,611	,000	,011
Tumor recurrence	,875	,837	,308	,470	,045	,759	,806	,031	,285	,085	,006	,671	,442
Distant metastasis	,570	,837	,268	,832	,075	,416	,271	,054	,866	,005	,915	,716	,728
	Gender	Tumor diameter	Tumor edge	SUVmax	PET/CT LN uptake	Side	Resection type	LN metastasis	Local invasion	First lavage	Last lavage	T stage	SUV group

Okada et al. state that cases with positive lavage cytology have worse prognosis and this is more apparent in cases with adenocarcinoma [5]. Likewise, our study showed that positive lavage cytology is a sign for poor prognosis in terms of local tumor recurrence and distant organ metastasis.

Although there are different views on etiology, the common aspect of the outcomes of all studies is that prognosis is worse in cases with positive lavage cytology. This situation causes upstaging in patients. Recently there has been an increase in studies on pleural lavage analysis and there is a need for standardization in lavage timing and sampling. We hope that positive lavage cytology, like malign effusion, will be accepted as a prognostic factor in staging as more studies based on wider series are conducted.

Competing interests

The authors declare that they have no competing interests.

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